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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/513,362	02/25/2000	Mark S Chee	A-67851-2/DJB/RMS/DCF	7034

7590 09/20/2002

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EXAMINER
STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
1637	17

DATE MAILED: 09/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/513,362	Applicant(s) CHEE ET AL.	
	Examiner Teresa E Strzelecka	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Office action is in response to an amendment filed on July 12, 2002.

Response to Arguments

2. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

However, Applicants arguments are not found to be persuasive. In this case, Navot et al. teach pyrosequencing of nucleic acids which may be attached to microbeads in an electrophoresis-free system, and attachment to the solid support provides confinement to the sample (col. 15, lines 1-14), and Walt et al. teach microbeads with attached nucleic acids, distributed randomly on the surface of the fiber optic bundle, creating an microbead array (col. 3, lines 35-45; col. 4, lines 35-38; col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array of the microbeads can be used for sequencing (col. 24, lines 51-52) (emphasis added).

Applicants argue that the motivation provided by Walt et al., namely, that using microbead arrays allowed separation of nucleic acid synthesis from their placement on the array and distributing beads randomly was fast and inexpensive, is not sufficient, since:

a) synthesis of nucleic acids being separated from their placement on the array is not equivalent to determining DNA sequence,

b) the synthesis of nucleic acids and distribution of beads on an array does not suggest any combination with a pyrosequencing method to determine the sequence of a target nucleic acid hybridized (?) to the bead,

c) neither reference suggests the desirability of combining the references,

d) the prior art references, alone or in combination, do not suggest the use of microspheres randomly distributed on a surface for sequencing a plurality of target nucleic acids by pyrosequencing or a method of sequencing nucleic acids by using a capture probe covalently attached to a microsphere randomly distributed on a surface of a substrate.

Navot et al. teach pyrosequencing of nucleic acids attached to a solid support (which may be a microbead) in an electrophoresis-free system, and Walt et al. teaches that the array of randomly distributed microbeads may be used for sequencing. Both references teach sequencing and nucleic acids attached to microbeads. Therefore, the motivation provided by Walt et al. is perfectly applicable, since it provides a motivation for a way of detection of sequencing reactions on microbeads of Navot et al. to be performed on an array which can be prepared quickly and inexpensively.

The art rejections are therefore maintained.

Priority

3. Applicants amended the first paragraph of the specification to correct an error in the application number. However, the provisional application number 60/160,027 is unrelated to the subject matter of the current application, being drawn to "Clothes dryer wall vent box".

Appropriate correction is required.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-4, 6-10, 12-17 and 22-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. (U.S. Patent No. 6,335,165 B1) and Walt et al. (U.S. Patent No. 6,327,410 B1).

A) Navot et al. teaches a method of sequencing GC-rich regions of nucleic acids, the method comprising contacting modified GC-rich nucleic acid with a sequencing primer, synthesizing a complementary strand in a stepwise manner, in which an identity of each incorporated nucleotide is determined, and determining the sequence of the GC-rich nucleic acid (col. 7, lines 10-29; col. 12, lines 34-46). The nucleotide addition is catalyzed by a DNA polymerase (the first enzyme) (col. 14, lines 46-67).

The identity of each incorporated oligonucleotide can be determined by monitoring a release of a pyrophosphate (PPi) group and the detection of PPi is achieved enzymatically. The PPi formed in the sequencing reaction is converted to ATP by ATP sulfurylase (second enzyme) and the ATP production is monitored by the firefly luciferase (third enzyme) (col. 7, lines 60-67; col. 4, lines 55-67; col. 5, lines 1-36; col. 12, lines 66-67; col. 13, lines 1-35).

Another way of determining the identity of an incorporated nucleotide is achieved by using nucleotide analogs, which include a removable blocking group at the 3'-OH

position and a removable reporter group. Following the addition of a nucleotide to the complementary strand the blocking group is removed to permit the addition of the next nucleotide. The removable reporter group allows identification of the incorporated nucleotide (col. 13, lines 43-67).

The target nucleic acid can be bound to a solid support either directly or indirectly, for example, through a capture probe (col. 10, lines 29-33). In another embodiment, either the sequencing primer or the target can be immobilized on beads (col. 15, lines 1-14).

B) Navot et al. do not teach microspheres (beads) randomly distributed on a surface of a substrate, where the substrate comprises discrete sites, and the discrete sites are wells. They do not teach the substrate being a fiber optic bundle.

Navot et al. teach a kit comprising amplification primers and a DNA polymerase (col. 6, lines 63-67; col. 7, lines 1-10; col. 9, lines 5-7).

C) Walt et al. teach microsphere-based analytical chemistry system in which the microspheres are distributed on a substrate which might be a fiber optic bundle (Abstract). The surface of the substrate comprises discrete sites into which at least two subpopulations of microspheres are distributed. Each of the microspheres comprises a bioactive agent and an optical signature which allows identification of the bioactive agent. The beads can be randomly distributed on the array (col. 3, lines 35-45; col. 4, lines 35-58). The bioactive agent attached to the microsphere can be a nucleic acid, particularly a nucleic acid probe (col. 8, lines 15-19; col. 9, lines 41-67; col. 10, lines 1-47). The array can be used for sequencing (col. 24, lines 51-52).

The substrate materials include glass, plastics and a variety of other materials. The surface of the substrate contains discrete sites, which might be wells, and the substrate may be a fiber optic bundle (col. 5, lines 32-46, lines 61-67; col. 6, lines 22-41).

Walt et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used microspheres randomly distributed on a substrate of Walt et al. as the beads in the pyrosequencing method of Navot et al. The motivation to do so, expressly provided by Walt et al., would have been that synthesis of nucleic acids was separated from their placement on the array and random distribution of beads was fast and inexpensive.

6. Claims 5 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Balch (U.S. Patent No. 6,083,763).

A) Claim 5 is drawn to the hybridization complexes comprising target sequences, sequencing primers, adapter probes and capture probes covalently attached to the microspheres. Claim 11 is drawn to a hybridization complex comprising capture probe, adapter probe and a target sequence.

B) Neither Navot et al. nor Walt et al. teach adapter probes.

C) Balch teaches molecular analysis aparatus for high-throughput analysis of molecular targets in complex mixtures. This apparatus can be used for DNA amplification and sequencing in an array format. (Abstract, Example III). Each location of the array

comprises a capture probe attached to a solid substrate (col. 17, lines 28-41; col. 18, lines 55-66). The target probes (adapter probes) are designed to be complementary to both the capture probes and the target nucleic acids (col. 20, lines 39-49; Fig. 5a). The capture probes can be used directly to form hybridization complexes with the target nucleic acid sequences (col. 21, lines 21-23).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the adapter probes of Balch for the formation of primer-target complexes in the combined method of Navot et al. and Walt et al. The motivation to do so, expressly provided by Balch, would have been that adapter probes a delivered unique binding domain for each site on an array.

7. Claims 18-21 and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navot et al. and Walt et al. as applied to claims 1 and 10 above, and further in view of Nyren et al. (WO 98/13523).

A) Claims 18-21 are drawn to a kit for nucleic acid sequencing comprising a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microsphres comprising capture probes, an extension enzyme, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

B) Navot et al. teaches a kit as described above, but does not teach a substrate with discrete sites, population of microspheres randomly distributed in these sites, the microsphres comprising capture probes, dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels. Walt

et al also teach a composition comprising a substrate with discrete sites (wells) and a population of microspheres randomly distributed in the wells, the microspheres comprising a bioactive agent (claims 1, 5, 9, 27 and 39), but does not teach dNTPs, a second enzyme for conversion of PPi to ATP, a third enzyme for the detection of ATP, and dNTPs with different labels.

C) Nyren et al. teach a kit comprising a sequencing primer, a polymerase, a detection enzyme means for identifying pyrophosphate release, dNTPs or ddNTPs (page 20, second paragraph; page 21, first paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have added kits of Nyren et al. to a kit and a composition disclosed by Navot et al. and Walt et al. The motivation to do so would have been that kits were conventional in the field of molecular biology and provided the benefits of convenience and cost-effectiveness for practitioners in the art.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

TS
September 19, 2002 TS

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
9/19/02